Claim 37, line 1, before "antibody" insert --essentially purified and isolated--; and

line 2, replace "recognizes" with --specifically binds--.

Claim 38, line 2, replace "contains and antibody" with --comprises a pharmaceutical carrier and a polyclonal or monoclonal antibody--; and

lines 2-3, delete "either of the".

Please add the following new claim:

--39. The polypeptide of claim 18, which is

Ala Lys Ile Cys Tyr Glu Ile Gly Asn Arg His.--

REMARKS

Claims 1-39 are pending in this application. Claims 18, 19, 34 and 37-39 are active and corresponds to the elected invention. Claims 1-17, 20-33 and 35-36 are withdrawn from consideration. Reconsideration of all the claims at this time is respectfully requested.

Helicobacter plyori is a Gram negative bacterium found in the stomach mucosa in man. These bacteria produce and excrete urease, an enzyme which causes injury to the gastric mucosa. The expression of urease is controlled by four genes (UreA, UreB, UreC and UreD), whereas 6 genes (ureA, ureB, ureE, ureF, ureG and ureH) are essential for urease activity. The present inventors have now isolated a DNA fragment containing several genes which encode accessory proteins.

Applicants include herewith a certified copy of the foreign priority document, FR 91 12198 (Attachment A). Footnotes (1) and (5) have been added to Table 2 on page 39 to make Table 2 consistent with the priority document (See Attachments B and C).

The rejection of the claims under 35 U.S.C. §102(b), or under 35 U.S.C. §103, over each of Mulrooney et al, Ferrero et al, Bradley et al or Tabaqchali et al is in part obviated by amendment and in part respectfully traversed.

Mulrooney et al cloned a 4.8kb DNA fragment from *Klebsiella aerogenes* which had six open reading frames: *ureA* (11.1 kDa), *ureB* (11.7 kDa), *ureC* (60.3 kDa), *ureE* (17.6 kDa), *ureF* (25.2 kDa) and *ureG* (21.9 kDa).

First, the DNA of the present invention was isolated from *Helicobacter plyori*, not *Klebsiella aerogenes*. None of the cited references equates these bacteria or suggests that the bacteria express structurally identical urease.

Second, none of the three peptides encoded by the accessory genes ureE, ureF or ureG which were described by Mulrooney et al have the same sequences as the presently claimed peptides. For example, in *Klebsiella aerogenes*, the ureE gene encodes a protein whose N-terminal sequence is MLYLTQ...; whereas in *Helicobacter plyori* the ureE gene encodes a protein whose N-terminal sequence is MIIERL...

Third, Mulrooney et al never isolated peptides; instead they only predicted the existence of the same based on the open reading frames present in the cloned DNA. Accordingly,

the peptides of the present invention are not anticipated by Mulrooney et al.

Ferrero et al is the present inventors own work. The reference was published in October 1991 - concurrently with the priority document for the present application. This reference is not available as prior art against the present application.

Bradley et al sequenced a 5.0 kb region from *Proteus mirabilis* which had six open reading frames: *ureA* (11.0 kDa), *ureB* (12.2 kDa), *ureC* (61.0 kDa), *ureD* (31.0 kDa), *ureE* (17.9 kDa) and *ureF* (23.0 kDa).

First, the DNA of the present invention was isolated from *Helicobacter plyori*, not *Proteus mirabilis*. None of the cited references equates these bacteria or suggests that the bacteria express structurally identical urease. In fact, based on differences between the sequences of proteins described by Bradley et al and Mulrooney et al, it does not appear that a high degree of sequence homology exists between bacterial strains. The only similarity noted by Bradley et al is between *Proteus mirabilis* and jack bean urease (a plant urease).

Second, neither of the peptides encoded by the accessory genes ureE or ureF which were described by Bradley et al have the same sequences as the presently claimed peptides. For example, in *Proteus mirabilis*, the ureE gene encodes a protein whose N-terminal sequence is MKKFTQ...(see figure 2, bp 3655 to 4137); whereas in *Helicobacter plyori* the ureE gene encodes a protein whose N-terminal sequence is MIIERL...

Third, Bradley et al never isolated peptides; instead they only predicted the existence of the same based on the open reading frames present in the cloned DNA. Accordingly, the peptides of the present invention are not anticipated by Bradley et al.

Tabaqchali et al describe probes which bind *Helicobacter plyori* UreA and UreB. The probes were designed from a gene fragment which did not include any of the accessory genes. In fact, Tabaqchali et al make no mention of accessory genes, UreE, UreF, UreG, UreH or UreI. It is interesting that none of the cited references make any mention of accessory genes UreH or UreI. The Examiner notes that part of the gene fragment isolated by Tabaqchali et al comprises a part of the nucleic sequence corresponding to UreI. While SEQ ID NO:1 of Tabaqchali et al does indeed include nucleotides 2622-2693, Tabaqchali et al fail to recognize that this stretch of DNA encodes anything.

The dissimilarity of the genes disclosed by Mulrooney et al and Bradley et al is discussed in Cussac et al, cited by the Examiner in his rejection under 35 U.S.C. §112, first paragraph. Cussac et al state that

> The degree and relatedness, in terms of the genetic organization and the polypeptides encoded was greatest between *P. mirabilis* and *K. aerogenes* vis-a-vis *H. pylori*. This has been the subject of a previous communication (16). While the UreG polypeptide of *H. pylori* was found to be highly similar to that of *K. aerogenes* (92% conservation and 59% identity), the degrees of similarity and identity between the UreE and UreF polypeptides of the bacteria were 33 and 14, and 44 and 11.6% respectively....The urease region of *H. pylori* exhibits some unique feature which are worthy of mention. First, the genes are designated UreI and ureH are unique to *H. pylori*. Second, the urease region consists of three blocks of genes that are transcribed in the same

> direction and have an intergenic region of 420 bp between ureD and ureA (16) and 200 bp between ureB and ureI; this compares with the *Klebsiella* and *Proteus* gene clusters that behave as single gene blocks (the largest intergenic regions being 11 bp [26] and 26 bp [24], respectively). these findings suggest a genetic organization peculiar to *H. pylori*, in which the three gene blocks might be regulated independently.

Thus, because Cussac et al teaches the uniqueness of the urease gene cluster in *H. pylori*, it supports the finding that the present invention cannot be anticipated by either of Mulrooney et al or Bradley et al. Further, Applicants note that the relatedness of different sequences, including those of H. pylori, could not be ascertained until the present invention. Applicants respectfully submit that the cited references could only be combined using hindsight.

As none of the cited references either alone or in combination anticipate or render the present invention obvious, Applicants submit that the rejection should be withdrawn.

Likewise the rejection of Claims 18 and 19 under 35 U.S.C. §103 over the above references further in view of Sevier et al is respectfully traversed. Sevier et al teaches the use of antibodies for immunotherapy and immunodiagnostics. A general teaching of monoclonal antibodies against clinically important antigens is disclosed in Table 2, page 1799. The list does not contain any urease from any source. Applicants submit that as the antigens of the present invention are neither anticipated nor obvious over Mulrooney et al, Ferrero et al, Bradley et al or Tabaqchali et al, this general teaching cannot render the claims obvious. Further the new

Biotechnology Process Law signed by President Clinton in November 1995, explicitly allows claims where antibodies against novel antigens are used in processes which were generally known. Accordingly, withdrawal of this rejection is respectfully requested.

The rejection of claim 37 under 35 U.S.C. §101 has been obviated by amendment, consistent with the Examiner's suggestion.

The rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully traversed. Cussac et al disclose that no role has been assigned to the nine proteins encoded by the *H. pylori* urease gene cluster. Although it is true that the exact role of each of these polypeptides is unclear, it has been definitively shown that each of these polypeptides must be expressed in their native form for proper urease activity. Thus Cussac et al does not demonstrate that the polypeptides of the present invention cannot be used as suggested in the present application.

Houghten et al generally teaches that modifications in the amino acid structure of an epitope can alter antigenic determinants. Houghten et al provides no teachings explicitly on antigens derived from urease genes. Applicants submit that in the face of their credible teaching that the antibodies of the present invention provide therapeutic benefits, the Examiner should provide reasons why their particular antibodies would not be expected to function as set forth in their specification.

The rejection of the claims under 35 U.S.C. §112, second paragraph, has in part been obviated by amendment and in part respectfully traversed. The polypeptide claimed corresponds to one of the polypeptides UreE, UreF, UreG, UreH, or UreI in Figure 4 or any part thereof which has attenuated activity. Fragment 209-282 is excluded from this group. Applicants are entitled to claim the subject matter of their invention in any way they desire so long as the claim language is definitive. Applicants submit that the present claim language is definitive and request that the Examiner specify what portion of the claims he believes is "indefinite". Further, the Applicants are not aware of any prohibition against functional or operational language. Applicants request that the Examiner cite support for the prohibition.

RESTRICTION REQUIREMENT

The Examiner has required restriction in the above-identified application and has divided the claims as follows:

Group I - Claims 1-17, 20-23, 29, 30, 35 and 36, drawn to DNA,

Group II - Claims 18, 19, 37 and 38, drawn to polypeptides and antibodies, and

Group III - Claims 24-28 and 31-34, drawn to host cells with mutant genes.

Applicants have elected, with traverse, Group II, for examination purposes only. Applicants note that at the time of their election, March 3, 1995, Claim 34 was grouped in Group II, not Group III as presently indicated on page 2 of the Official Action. Applicants are assuming this claim is

currently being examined consistent not only with their election but also as indicated in Part II.4 of page 1 of the Official Action. Clarification is requested.

The present application is a PCT application. The requirements for restriction are different than those for applications filed directly with the U.S. Patent and Trademark Office. According to 37 C.F.R. §1.488, if an international application does not comply with the requirement of unity of an invention, the Applicant may be invited to restrict the claims. The burden is on the U.S. Patent and Trademark Office to provide reasons and/or examples to support any allegations of lack of unity of invention.

Applicants respectfully traverse the Restriction Requirement on the grounds that no lack of unity of invention has been established. Instead the Examiner has applied a restriction requirement in accordance with 35 U.S.C. §121. Accordingly, Applicants respectfully request withdrawal of this requirement. Applicants believe they are entitled to examination of claims drawn to DNA, proteins encoded thereby, antibodies to said proteins and methods of using said antibodies, consistent with the definition of unity of invention provided by 37 C.F.R. §1.475. The special technical feature of this invention is genes associated with urease activity. Applicants respectfully request that the Restriction Requirement be withdrawn.

Applicants submit the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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